

Emergency Department Workflow Times of Intravenous Thrombolysis with Tenecteplase versus Alteplase in Acute Ischemic Stroke: A Prospective Cohort Study before and during the COVID-19 Pandemic

Matias Guzman^{a, b, c} Pablo M. Lavados^{a, b, c} Gabriel Cavada^d
Alejandro M. Brunser^{a, b} Veronica V. Olavarria^{a, b}

^aUnidad de Neurología Vascular, Servicio de Neurología, Departamento de Neurología y Psiquiatría, Clínica Alemana de Santiago, Vitacura, Chile; ^bServicio de Neurología, Hospital Padre Hurtado, Servicio de Salud Metropolitano Sur Oriente, Santiago, Chile; ^cFacultad de Medicina Clínica Alemana Universidad del Desarrollo, Santiago, Chile; ^dUnidad de Investigación y Ensayos Clínicos, Departamento de Desarrollo Académico e Investigación, Clínica Alemana de Santiago, Santiago, Chile

Keywords

Ischemic stroke · Cerebrovascular disease · Thrombolytic therapy · Door-to-needle time · Length of stay · Door-to-groin puncture time · Tissue plasminogen activator · Tenecteplase

Abstract

Introduction: Tenecteplase (TNK) has demonstrated to be non-inferior to alteplase (ALT) for intravenous thrombolysis (IVT) in acute ischemic stroke (AIS). There are potential workflow benefits associated with TNK use, aiming to reduce patient length of stay in the emergency department. Our aim was to investigate whether the routine use of TNK during the COVID-19 pandemic influenced workflow times compared to historical use of ALT, while maintaining non-inferior clinical outcomes in a non-drip and ship scenario of a comprehensive stroke center. **Methods:** We included patients with AIS admitted from September 2019 to September 2022 and compared those treated with TNK during the

COVID-19 pandemic to those treated with ALT in the period immediately before. We compared emergency department length of stay (EDLOS), door-to-needle time (DTN), door-to-groin puncture time (DTG), clinical and safety outcomes with adjusted general linear regression models. **Results:** 110 patients treated with TNK and 111 with ALT were included in this study. Mean EDLOS was 251 (SD = 164) min for TNK users versus 240 (SD = 148) min for ALT ($p = 0.62$). Mean DTN was 43 (SD = 25) min for TNK versus 46 (SD = 27) min for ALT users ($p = 0.39$). Mean DTN under 60 min was achieved in 86 (78.2%) patients and in 85 (76.5%) patients of the TNK and ALT groups, respectively ($p = 1.0$). DTN under 45 min was achieved in 65.4% and 58.6% ($p = 0.65$) of the TNK and ALT groups, respectively. DTG time was 114 (SD = 43) min for TNK versus 111 (SD = 58) min in the ALT group ($p = 0.88$). DTG under 90 min was achieved in 32% of the TNK group and 35% of the ALT group ($p = 0.69$). There were no differences in any of the clinical or safety outcomes between groups at 90 days. **Conclusions:** The adoption of TNK during COVID-19 pandemic did not result in a change in EDLOS,

DTN, or DTG times when compared to ALT in this cohort. Safety and clinical outcomes were similar between groups. Probably a greater benefit could have been seen in a drip and ship thrombolysis setting. Further research is needed to assess the potential advantages of TNK in drip and ship scenarios of IVT.

© 2025 The Author(s).

Published by S. Karger AG, Basel

Plain Language Summary

This study compares two medications, tenecteplase (TNK) and alteplase (ALT), used to treat patients with acute ischemic stroke. TNK has potential workflow advantages because it is quicker and easier to administer. TNK could reduce the time patients spend in the emergency department and improve the time it takes to start treatment (door-to-needle time) or perform additional procedures like thrombectomy (door-to-groin time), compared to ALT. The study included 221 patients: 110 received TNK, and 111 received ALT. The results showed no significant difference in the time patients spent in the emergency department or the time taken to start treatment between the two groups. Both drugs had similar safety and effectiveness, with no major differences in patient recovery or complications like bleeding. While TNK did not significantly reduce emergency workflows, it is still a safe and effective alternative to ALT in this clinical setting.

© 2025 The Author(s).

Published by S. Karger AG, Basel

Introduction

Alteplase (ALT) is currently the most widely used approved intravenous thrombolysis (IVT) treatment of acute ischemic stroke (AIS). Tenecteplase (TNK) a modified version of ALT, offers a longer half-life and higher specificity to fibrin. It has proved to be as safe and effective compared to ALT for the treatment for AIS, offering various advantages including reduced preparation and administration times, requiring only single rapid bolus with no need for continuous infusions, thus facilitating the transfer of patients requiring endovascular treatment [1, 2].

Systematic reviews and meta-analyses suggest that TNK, when used before thrombectomy, is associated with a greater degree of early reperfusion in large vessel occlusions (LVO) while maintaining non-inferiority compared to ALT in terms of efficacy and safety [1–9]. TNK use has been recently included in current clinical guidelines as an alternative to ALT and recent meta-

analysis suggests it might be superior to ALT [1, 2, 10–17].

The ACT trial demonstrated non-inferiority of TNK in standard reperfusion window (<4.5 h) including patients requiring thrombectomy [10]. The TRACE 2 trial also demonstrated non-inferiority of TNK in standard reperfusion window in patients non eligible to mechanical thrombectomy [18]. However, TIMELESS trial investigating TNK in anterior (LVO) versus placebo in extended window (4.5–24 h) using perfusion imaging selection, failed to demonstrate clinical benefit [19]. Recently, the TRACE 3 study has increased even more extended window thrombolysis threshold, showing clinical efficiency and safety up to 24 h in perfusion selected patients who had no access to thrombectomy [20].

Cohort studies have previously shown a reduction in door-to-needle time (DTN), with reduction in overall hospitalization costs using TNK [21–24]. Nevertheless, there is limited evidence on the impact of TNK use on overall reperfusion times and emergency department patient length of stay (EDLOS). Our aim was to investigate whether the routine use of TNK during the COVID-19 pandemic impacted the emergency department workflow times while maintaining safety and clinical outcomes in a non-drip and ship scenario of a comprehensive stroke center. We hypothesized that routine TNK use would be associated with a reduction in ED workflow times with similar clinical and safety outcomes compared to those that used ALT before the switch to TNK.

Methods

Study Design, Setting and Participants

In this cohort study, we analyzed data from our prospective stroke registry (Registro de Enfermedades Cerebrovasculares Clínica Alemana de Santiago [RECA]), which include all admitted AIS, adult patients (aged ≥ 18 years) who consent. Our institution is an academic nonprofit private medical center in Santiago, Chile. We included consecutive AIS patients presenting in the (ED) and who were treated with ALT or TNK between September 2019 and September 2022.

Variables, Data Sources, and Procedures

AIS was defined as an episode of neurological dysfunction caused by focal cerebral infarction according to the current standard definitions [25, 26]. Vascular risk factors were defined as follows: hypertension (a history of treated hypertension or current use of antihypertensive

medication); diabetes (a history of diabetes or current treatment for diabetes mellitus); coronary-artery disease (history of angina, acute myocardial infarction, or coronary revascularization); congestive heart failure (history of or current treatment for congestive heart failure); atrial fibrillation (known previous atrial fibrillation, presently diagnosed or current treatment for atrial fibrillation); hypercholesterolemia (history of or current treatment for hypercholesterolemia); smoking (current smoker); and alcohol consumption (current moderate or heavy drinker was defined as 50 g per day, equivalent to 500 mL or two drinks of wine, 1,000 mL of beer, or 5 units of spirits, or being intoxicated at least once a week) [27]. We excluded patients with stroke mimics, spinal cord, or retinal infarctions. All variables were prospectively collected and transferred to an electronic database REDCap electronic data capture tools hosted at Clínica Alemana de Santiago. REDCap (Research Electronic Data Capture, Vanderbilt University, Nashville, TN, USA).

Stroke Code

Patients with stroke symptoms upon arrival at the ED are evaluated by a neurologist on duty at all hours. The institutional stroke code is activated when patient arrive within 24 h of symptom onset. The imaging protocol includes brain CT, brain and neck CT angiogram, DWI-MRI in selected patients. Patients arriving within 4.5 h of symptom onset, with no evidence of hemorrhage on CT, were treated with IVT. Wake-up strokes or symptoms of unknown onset received IVT when significant DWI-MRI/FLAIR MRI mismatch or a large penumbra in CT perfusion was identified [2–4]. Mechanical thrombectomy was performed when (LVO) was identified, involving the internal carotid, middle cerebral artery (M1-M2) or basilar artery, within a timeframe of less than 6 h, following conventional recommendations. For cases involving more distal occlusions or other vessels, decisions were taken on a case-by-case basis. In cases eligible for extended window thrombectomy, the DAWN and DEFUSE 3 criteria were employed [5, 6]. In such cases, IVT was administered within 9 h if a favorable mismatch was identified.

We initiated TNK use for IVT in September 2019 and rapidly transitioned to TNK in the first months of 2020 as the standard stroke thrombolytic therapy, driven by the COVID-19 pandemic because of potential workflow advantages in reducing (EDLOS) and after an institutional protocol modification, supported by the Chilean ministry of health. Patients treated with IVT received either 0.25 mg/kg dose of TNK or 0.9 mg/kg ALT (10% in bolus and the rest infused in an hour). Some cases were treated with 0.6 mg/kg of ALT if determined by the attending neurologist, based on

a suspected elevated risk of symptomatic hemorrhagic transformation. Patients' 90-day modified Rankin scores (mRS) were collected through telephone interviews conducted by a non-medically trained professional, not related to this study, or using the patients' available clinical data obtained in usual clinical follow-ups.

Outcomes

Primary Outcomes (Workflow Times)

EDLOS, DTN, DTN <45 min, and DTN <60 min, door-to-groin puncture time (DTG) and DTG <90 min.

Secondary Outcomes (Clinical)

Excellent functional outcome defined as mRS 0–1 at 3 months; good functional outcome defined as mRS 0–2 at 3 months.

Safety Outcomes

Any intracerebral hemorrhage, symptomatic intracerebral hemorrhage (ECAS3 criteria: any intracranial hemorrhage associated with an increase of 4 patients in NIHSS), fatal hemorrhage and all-cause mortality during hospitalization.

Analysis

Descriptive statistics were performed comparing treatment groups using chi-square and Fisher's exact tests, as appropriate, with 2-sided *p* values. The Mann-Whitney U test was employed for non-normally distributed continuous variables in the univariate analyses. To examine the association of the thrombolytic agent with workflow outcomes (EDLOS, DTN, and DTG), generalized linear regression models were utilized for gamma distribution. Covariates for adjustment included age, sex, arrival NIHSS and ASPECTS scores, presence of previous stroke, previous mRS, anticoagulation use during the last month, arrival glucose levels, systolic blood pressure at arrival, LVO, and utilization of mechanical thrombectomy. Additional covariates were adjusted only if they showed significant differences between groups. We also used generalized linear models to assess clinical outcomes, covariates were adjusted if exhibited significant differences between groups. Hypothesis testing for the primary and secondary analyses employed a significance level of 5% ($\alpha = 0.05$). In-hospital stroke patients were excluded from analysis. Missing values were imputed for the analysis based on a lineal regression method, assuming normal multivariant distribution. All statistical analyses were conducted using Stata 18.0. The paper's reporting adheres to the STROBE guidelines.

Table 1. Baseline demographic and clinical characteristics of the entire cohort of patients treated with thrombolysis

	TNK (<i>n</i> = 110)	ALT (<i>n</i> = 111)	<i>p</i> value
Age, years, mean (SD)	67.55 (17)	70.28 (17)	0.22
Male sex, <i>n</i> (%)	59 (53.6)	67 (60.4)	0.50
Baseline Rankin score, median (IQR)	0 (0–4)	0 (0–4)	0.42
Hypertension, <i>n</i> (%)	63 (57.3)	74 (66.7)	0.24
Diabetes mellitus, <i>n</i> (%)	11 (10.0)	18 (16.2)	0.23
Atrial fibrillation, <i>n</i> (%)	11 (10.0)	15 (13.5%)	0.53
Anticoagulant use during last month, <i>n</i> (%)	4 (3.6)	6 (5.4)	0.74
Previous heart attack, <i>n</i> (%)	13 (11.8)	13 (11.7)	0.61
Cardiopathy, <i>n</i> (%)	31 (28.2)	39 (35.1)	0.39
Dyslipidemia, <i>n</i> (%)	44 (40.0)	43 (38.7)	0.78
Tobacco use, <i>n</i> (%)	30 (27.3)	48 (43.2)	0.02
Previous stroke, <i>n</i> (%)	13 (11.8)	15 (13.5)	0.84
Known symptom onset, <i>n</i> (%)	103 (93.6)	107 (96.4)	1.0
Blood glucose, mg/dL, mean (SD)	115 (116)	119 (168)	0.35
Systolic blood pressure, mm Hg, mean (SD)	152 (116)	153 (91)	0.86
CT ASPECTS, median (IQR)	10 (7–10)	10 (4–10)	0.2
NIHSS, median (IQR)	6 (0–27)	5 (0–33)	0.3
Large vessel occlusion, <i>n</i> (%)	44 (40.0)	40 (36.0)	0.78
Middle cerebral artery M1 occlusion, <i>n</i> (%)	25 (22.7)	24 (21.6)	1.00
Middle cerebral artery M2 artery occlusion, <i>n</i> (%)	24 (21.8)	17 (15.3)	0.30
Internal carotid artery occlusion, <i>n</i> (%)	12 (10.9)	4 (3.6)	0.06
Basilar artery occlusion, <i>n</i> (%)	3 (2.7)	1 (0.9)	0.62
Symptom to door time, min, mean (SD)	117 (147)	117 (119)	1.0
Conventional cerebral angiography, <i>n</i> (%)	30 (27.3)	20 (18.0)	0.10
Mechanical thrombectomy, <i>n</i> (%)	25 (22.7)	14 (12.6)	0.05

Data are mean (SD), median (IQR), or *N* (%). IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale.

Results

From September 2019 to September 2022, a total of 221 patients were treated with IVT, 110 with TNK and 111 patients with ALT. During the implementation period, there was widely agreement among physicians and nurses that TNK administration was easier and faster compared to ALT.

Baseline characteristics are displayed in Table 1. Cohorts were well balanced regarding patients' basal characteristics, with only a higher rate of tobacco use in the ALT group (43.2% vs. 27.3%) ($p = 0.02$). Times

between symptom onset and arrival at the hospital (symptom to door times) were found to be the same in both treatment groups. Stroke-related variables were well balanced. The rate of LVO was similar in both groups (40% vs. 36%) ($p = 0.78$). The TNK group had a slightly higher but no significant rate of internal carotid occlusions ($p = 0.06$). Consequently, the TNK group had more angiographies and thrombectomies, only the latter being statistically significant (22.7% vs. 12.6%) ($p = 0.05$).

Primary outcomes are reported in Table 2. There was no significant difference in mean EDLOS being 251 min in TNK versus 240 min in the ALT group ($p = 0.62$). The only

Table 2. Primary outcomes

	TNK, <i>N</i> = 110	ALT, <i>N</i> = 111	B coefficient (SE) or odds ratio (95% CI)	<i>p</i> value
Emergency department length of stay time, min, mean (SD)	251 (164)	240 (148)	10.4 (21.2)	0.62
DTN time, min, mean (SD)	43 (25)	46 (27)	−3.01 (3.53)	0.39
DTN time <60 min, <i>n</i> (%)	86 (78.2)	85 (76.5)	0.99 (0.50–1.99)	1.0
DTN time <45 min, <i>n</i> (%)	72 (65.4)	65 (58.6)	1.1 (0.6–2.1)	0.65
DTG time, min, mean (SD)	114 (43)	111 (58)	2.21 (15.0)	0.88
DTG time <90 min, <i>n</i> (%)	8 (32)	7 (35)	0.67 (0.1–4.5)	0.69

Data are mean (SD) and *N* (%). DTN, door-to-needle; DTG, door-to-groin puncture.

variable associated with a lower EDLOS being indication of angiography due to LVO ($p = 0.01$) (online suppl. Table S1; for all online suppl. material, see <https://doi.org/10.1159/000543900>). The mean DTN was 43 min in TNK versus 46 min in ALT ($p = 0.39$). There was no difference between groups in DTN <60 min ($p = 1.0$) or < 45 min ($p = 0.65$). The variables associated with lower DTN time were a higher NIHSS and no anticoagulation use. No differences were found in DTG median time ($p = 0.88$) or DTG <90 min achievement ($p = 0.69$). Increasing age, ASPECTS score and previous stroke were associated with increased DTG times (Table 3). Table 3 describes 3 month functional and safety outcomes. mRS was not available at follow-up in 13 patients (1 in ALT and 12 in TNK groups). There were no differences in functional outcome or safety among groups. Symptomatic intracranial hemorrhage occurred in low rates and was not different between groups. One patient in the ALT group had a fatal hemorrhage. All-cause mortality during hospitalization was nonsignificantly higher in the ALT group.

Discussion

We did not find any significant differences between TNK and ALT across the three primary outcomes: EDLOS, DTN, or DTG times. A plausible explanation for the absence differences in workflow times post-transition to TNK could be due to the limitation of small sample size and the implementation of safety measures prompted by the COVID-19 pandemic. These measures included the use of protective safety gear, stringent asepsis protocols before imaging, mandatory negative PCR rapid testing, pre-hospitalization chest CT scans, and reduced avail-

ability of intensive care unit (ICU) beds during the pandemic period. These factors and safety protocols may have limited the potential impact of TNK on reducing workflow times. Our findings contrast with previous evidence in which TNK was associated with reduced DTN and door-in-door-out times [21, 23]. Another potential factor is that previously reported benefits of TNK in DTG times are described in emergency medical systems where ground transportation is initiated only after completing ALT infusion. Consequently, TNK might yield greater benefits in patients needing transfer to another center for mechanical thrombectomy, a scenario not applicable to our patient cohort. It is noteworthy that our center's baseline workflow times are low. Furthermore, our DTG times were lower than previous reported needle-to-groin times, in this context, the efficiency of our workflow times makes it difficult to find significant improvements in small sample sizes (17,19). Our study aligns with the results of the TRACE 2 and ACT that showed non-inferiority of ALT compared to TNK regarding functional outcomes. The ROSE-TNK trial suggests that intravenous TNK within 4.5–24 h of onset may be safe and feasible in AIS patients with a DWI-FLAIR mismatch [28]. In the CERTAIN trial, TNK showed lower odds of symptomatic ICH when compared with ALT [12].

Our findings support considering TNK as a valid and safe option for patients who require extended window thrombolysis and extended thrombectomy. These are in accordance with EXTEND, WAKE UP, ECAS IV, DAWN, and DEFUSE 3 studies, although only using ALT (2–4). Regarding safety results, in our cohort there were no differences in hemorrhagic transformation as shown in other studies.

Table 3. Functional and safety outcomes

	TNK, <i>N</i> = 110	ALT, <i>N</i> = 111	B coefficient (SE) or odds ratio (95% CI)	<i>p</i> value
mRS at 3 months, median (IQR)	1 (0–6)	1 (0–6)	1.02 (0.60–1.74)	0.94
mRS (0–1) at 3 months, <i>n</i> (%)	66 (65.3)	67 (57.8)	1.43 (0.81–2.51)	0.81
mRS (0–2) at 3 months, <i>n</i> (%)	77 (76.2)	79 (68.1)	1.39 (0.83–2.86)	0.68
Hemorrhagic transformation, <i>n</i> (%)	13 (12.1)	8 (7.6)	1.67 (0.67–4.24)	0.27
Symptomatic intracranial hemorrhage, <i>n</i> (%)	3 (2.7)	1 (1.1)	–	–
Fatal hemorrhage, <i>n</i> (%)	0 (0)	1 (1.2)	–	–
All-cause mortality during hospitalization, <i>n</i> (%)	2 (1.8)	7 (5.9)	0.28	0.172

Data are mean (SD), median (IQR), or *N* (%). Symptomatic intracranial hemorrhage according to ECASS III definition of any hemorrhage with neurologic deterioration, as indicated by an NIHSS score that was higher by 4 points or more than the value at baseline or the lowest value in the first 7 days, or any hemorrhage leading to death. IQR, interquartile range; mRS, modified Rankin Scale.

Our study has several limitations inherent to an observational study that can introduce bias such as: small sample size and the implementation of TNK during the COVID-19 pandemic, in which overall ED protocols were modified compared to previous periods, resulting in increased overall attention times. Another potential limitation is that we only included patients treated in a single comprehensive center, without treating in a drip and ship thrombolysis model. Unfortunately, we did not assess LVO recanalization rates between groups because we do not perform control angiograms in our patients after IVT or mechanical thrombectomy, thus that information is not available in our center database. Nevertheless, it offers several strengths, including the prospective data gathering, consecutive inclusion of treated patients to minimize selection bias, well-matched study groups, and small data loss. We were able to include a diverse patient cohort of stroke patients undergoing reperfusion therapy across various scenarios (thrombolytic treatment, combined with thrombectomy, extended reperfusion window, unknown stroke onset, and direct oral anticoagulant users).

Our study's results reinforce TNK as a suitable treatment choice for patients meeting these criteria, ensuring that they receive effective and safe care. It provides valuable insights into the potential benefits and safety of utilizing TNK in specific patient populations, shedding light on its potential to improve patient outcomes and functional independence within the context of extended treatment windows. These findings suggest also that treatment with ALT remains a solid choice for patients who will not be shipped to another center for thrombectomy.

These results and observations underscore the complexity of evaluating the real-world impact of a treatment switch like the one we studied, especially in the context of external factors such as the COVID-19 pandemic and variations in center-specific protocols; therefore, results should not be generalized to all clinical settings. While our results did not reveal the same improvements in workflow times as previous reports, they contribute valuable insights into the multifaceted nature of healthcare interventions and their outcomes. Further research may be needed to better understand the factors contributing to the differing results between our data and previous reports.

Conclusions

In routine clinical practice, the adoption of TNK in our cohort during COVID-19 pandemic did not result in a reduction in EDLOS, DTN, or DTG times when compared to ALT. Probably greater benefit could be seen in a drip and ship thrombolysis setting. These findings were accompanied by comparable safety and clinical outcomes between studied groups. Further research is needed to assess the potential advantages of TNK in specific subpopulations of AIS patients.

Acknowledgments

We thank patients and their families in our institution for authorizing the study of their medical records in pursuit of scientific knowledge.

Statement of Ethics

The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. This study protocol was reviewed and approved by Comité Ético Científico de la Facultad de Medicina, Clínica Alemana Universidad del Desarrollo ID N°36, Approval No. 2010-11, written informed consent was obtained and signed by every participant patient or their parent/legal guardian as local regulatory law requests.

Conflict of Interest Statement

Matias Guzman reports lectures supported by Boehringer Ingelheim. Gabriel Cavada has no conflicts of interest to declare. Alejandro M Brunser reports lectures supported by Boehringer Ingelheim. Veronica V. Olavarria reports receiving research grant from Boehringer Ingelheim and Clínica Alemana de Santiago during the conduct of the study. Pablo M. Lavados reports research support from Clínica Alemana and Boehringer Ingelheim, research grants from The George Institute and Clínica Alemana de Santiago during the conduct of the study; unrestricted research grants from Boehringer Ingelheim; personal fees from AstraZeneca and a Chilean Government research grant for the ÑANDU project outside the submitted work.

Funding Sources

The RECCA cohort has been funded by unconditional research grants from Clínica Alemana de Santiago, Lundbeck Chile, and Boehringer Ingelheim. The sponsors had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Author Contributions

M.G., P.M.L., and V.V.O.: contributed to the design, interpretation of the data and drafted the manuscript; M.G. and A.M.B.: contributed to the data collection of the study; M.G., G.C., and P.M.L.: performed the statistical analysis; P.M.L., G.C., A.M.B., and V.V.O.: contributed to interpreting results, reviewing the manuscript and approved the final version of the manuscript. V.V.O. has primary responsibility for final content.

Data Availability Statement

The datasets used and/or analyzed during the current study are not publicly available due to center internal policies but are available from the corresponding author on reasonable request.

References

- 1 Campbell BCV, Mitchell PJ, Churilov L, Yassi N, Kleinig TJ, Dowling RJ, et al. Tenecteplase versus alteplase before thrombectomy for ischemic stroke. *N Engl J Med*. 2018;378(17):1573–82. <https://doi.org/10.1056/NEJMoa1716405>
- 2 Campbell BCV, Mitchell PJ, Churilov L, Yassi N, Kleinig TJ, Dowling RJ, et al. Effect of intravenous tenecteplase dose on cerebral reperfusion before thrombectomy in patients with large vessel occlusion ischemic stroke: the EXTEND-IA TNK Part 2 randomized clinical trial. *JAMA*. 2020;323(13):1257–65. <https://doi.org/10.1001/jama.2020.1511>
- 3 Kobeissi H, Ghozy S, Turfe B, Bilgin C, Kadirvel R, Kallmers DF, et al. Tenecteplase vs. alteplase for treatment of acute ischemic stroke: a systematic review and meta-analysis of randomized trials. *Front Neurol*. 2023;14:1102463.
- 4 Rose D, Cavalier A, Kam W, Cantrell S, Lusk J, Schrag M, et al. Complications of intravenous tenecteplase versus alteplase for the treatment of acute ischemic stroke: a systematic review and meta-analysis. *Stroke*. 2023;54(5):1192–204. <https://doi.org/10.1161/STROKEAHA.122.042335>
- 5 Abuelazm M, Seri AR, Awad AK, Ahmad U, Mahmoud A, Albazee E, et al. The efficacy and safety of tenecteplase versus alteplase for acute ischemic stroke: an updated systematic review, pairwise, and network meta-analysis of randomized controlled trials. *J Thromb Thrombolysis*. 2023;55(2):322–38. <https://doi.org/10.1007/s11239-022-02730-5>
- 6 Abuelazm M, Seri AR, Awad AK, Ahmad U, Mahmoud A, Albazee E, et al. The efficacy and safety of tenecteplase versus alteplase for acute ischemic stroke: an updated systematic review, pairwise, and network meta-analysis of randomized controlled trials. *J Thromb Thrombolysis*. 2023;55(2):322–38. <https://doi.org/10.1007/s11239-022-02730-5>
- 7 Ma P, Zhang Y, Chang L, Li X, Diao Y, Chang H, et al. Tenecteplase vs. alteplase for the treatment of patients with acute ischemic stroke: a systematic review and meta-analysis. *J Neurol*. 2022;269(10):5262–71. <https://doi.org/10.1007/s00415-022-11242-4>
- 8 Seners P, Caroff J, Chausson N, Turc G, Denier C, Piotin M, et al. Recanalization before thrombectomy in tenecteplase vs. alteplase-treated drip-and-ship patients. *J Stroke*. 2019;21(1):105–7. <https://doi.org/10.5853/jos.2018.01998>
- 9 Katsanos AH, Psychogios K, Turc G, Sacco S, De Sousa DA, De Marchis GM, et al. Off-Label use of tenecteplase for the treatment of acute ischemic stroke: a systematic review and meta-analysis. *JAMA Netw Open*. 2022;5(3):E224506. <https://doi.org/10.1001/jamanetworkopen.2022.4506>
- 10 Menon BK, Buck BH, Singh N, Deschaintre Y, Almekhlafi MA, Coutts SB, et al. Intravenous tenecteplase compared with alteplase for acute ischaemic stroke in Canada (ACT): a pragmatic, multicentre, open-label, registry-linked, randomised, controlled, non-inferiority trial. *Lancet*. 2022;400(10347):161–9. [https://doi.org/10.1016/S0140-6736\(22\)01054-6](https://doi.org/10.1016/S0140-6736(22)01054-6)
- 11 Albers GW, Campbell BCV, Lansberg MG, Broderick J, Butcher K, Froehler MT, et al. A Phase III, prospective, double-blind, randomized, placebo-controlled trial of thrombolysis in imaging-eligible, late-window patients to assess the efficacy and safety of tenecteplase (TIMELESS): rationale and design. *Int J Stroke*. 2023;18(2):237–41. <https://doi.org/10.1177/17474930221088400>
- 12 Warach SJ, Ranta A, Kim J, Song SS, Wallace A, Beharry J, et al. Symptomatic intracranial hemorrhage with tenecteplase vs alteplase in patients with acute ischemic stroke: the comparative effectiveness of routine tenecteplase vs alteplase in acute ischemic stroke (CERTAIN) collaboration. *JAMA Neurol*. 2023;80(7):732–8. <https://doi.org/10.1001/jamaneurol.2023.1449>
- 13 Li S, Pan Y, Wang Z, Liang Z, Chen H, Wang D, et al. Safety and efficacy of tenecteplase versus alteplase in patients with acute ischaemic stroke (TRACE): a multicentre, randomised, open label, blinded-endpoint (PROBE) controlled phase II study. *Stroke Vasc Neurol*. 2022;7(1):47–53. <https://doi.org/10.1136/svn-2021-000978>

- 14 Kvistad CE, Næss H, Helleberg BH, Idicula T, Hagberg G, Nordby LM, et al. Tenecteplase versus alteplase for the management of acute ischaemic stroke in Norway (NOR-TEST 2, part A): a phase 3, randomised, open-label, blinded endpoint, non-inferiority trial. *Lancet Neurol.* 2022;21(6):511–9. [https://doi.org/10.1016/S1474-4422\(22\)00124-7](https://doi.org/10.1016/S1474-4422(22)00124-7)
- 15 Logallo N, Novotny V, Assmus J, Kvistad CE, Altelheld L, Rønning OM, et al. Tenecteplase versus alteplase for management of acute ischaemic stroke (NOR-TEST): a phase 3, randomised, open-label, blinded endpoint trial. *Lancet Neurol.* 2017;16(10):781–8. [https://doi.org/10.1016/S1474-4422\(17\)30253-3](https://doi.org/10.1016/S1474-4422(17)30253-3)
- 16 Wang Y, Cai X, Fang Q, Zhu J. Efficacy and safety outcomes of Tenecteplase versus Alteplase for thrombolysis of acute ischemic stroke: a meta-analysis of 9 randomized controlled trials. *J Neurol Sci.* 2024;458:122912. <https://doi.org/10.1016/j.jns.2024.122912>
- 17 Ma Y, Xiang H, Busse JW, Yao M, Guo J, Ge L, et al. Tenecteplase versus alteplase for acute ischemic stroke: a systematic review and meta-analysis of randomized and non-randomized studies. *J Neurol.* 2024;271(5):2309–23. <https://doi.org/10.1007/s00415-024-12243-1>
- 18 Wang Y, Li S, Pan Y, Li H, Parsons MW, Campbell BCV, et al. Tenecteplase versus alteplase in acute ischaemic cerebrovascular events (TRACE-2): a phase 3, multicentre, open-label, randomised controlled, non-inferiority trial. *Lancet.* 2023;401(10377):645–54. [https://doi.org/10.1016/S0140-6736\(22\)02600-9](https://doi.org/10.1016/S0140-6736(22)02600-9)
- 19 Albers GW, Juma M, Purdon B, Zaidi SF, Streib C, Shuaib A, et al. Tenecteplase for stroke at 4.5 to 24 hours with perfusion-imaging selection. *N Engl J Med.* 2024;390(8):701–11. <https://doi.org/10.1056/NEJMoa2310392>
- 20 Xiong Y, Campbell BCV, Schwamm LH, Meng X, Jin A, Parsons MW, et al. Tenecteplase for ischemic stroke at 4.5 to 24 hours without thrombectomy. *N Engl J Med.* 2024;391(3):203–12. <https://doi.org/10.1056/NEJMoa2402980>
- 21 Mahawish K, Gommans J, Kleinig T, Lallu B, Tyson A, Ranta A. Switching to tenecteplase for stroke thrombolysis: real-world experience and outcomes in a regional stroke network. *Stroke.* 2021;52(10):e590–3. <https://doi.org/10.1161/STROKEAHA.121.035931>
- 22 Warach SJ, Saver JL. Stroke thrombolysis with tenecteplase to reduce emergency department spread of coronavirus disease 2019 and shortages of alteplase. *JAMA Neurol.* 2020;77(10):1203–4. <https://doi.org/10.1001/jamaneurol.2020.2396>
- 23 Warach SJ, Dula AN, Milling TJ, Miller S, Allen L, Zuck ND, et al. Prospective observational cohort study of tenecteplase versus alteplase in routine clinical practice. *Stroke.* 2022;53(12):3583–93. <https://doi.org/10.1161/strokeaha.122.038950>
- 24 Gerschenfeld G, Liegey JS, Laborne FX, Yger M, Lyon V, Checkouri T, et al. Treatment times, functional outcome, and hemorrhage rates after switching to tenecteplase for stroke thrombolysis: insights from the TETRIS registry. *Eur Stroke J.* 2022;7(4):358–64. <https://doi.org/10.1177/23969873221113729>
- 25 Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ, Culebras A, et al. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* 2013;44(7):2064–89. <https://doi.org/10.1161/STR.0b013e318296aeca>
- 26 Williams L, Wilkins L. Correction to: an updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* 2019;50(8):E239.
- 27 Lavados PM, Hoffmeister L, Moraga AM, Vejar A, Vidal C, Gajardo C, et al. Incidence, risk factors, prognosis, and health-related quality of life after stroke in a low-resource community in Chile (ÑANDU): a prospective population-based study. *Lancet Glob Health.* 2021;9(3):e340–51. [https://doi.org/10.1016/S2214-109X\(20\)30470-8](https://doi.org/10.1016/S2214-109X(20)30470-8)
- 28 Wang L, Dai Y-J, Cui Y, Zhang H, Jiang C-H, Duan Y-J, et al. Intravenous tenecteplase for acute ischemic stroke within 4.5–24 hours of onset (ROSE-TNK): a phase 2, randomized, multicenter study. *J Stroke.* 2023;25(3):371–7. <https://doi.org/10.5853/jos.2023.00668>